Di Luca Daniel G. (Orcid ID: 0000-0002-1356-4919)
Olszewska Diana Angelika (Orcid ID: 0000-0002-1814-8834)
Mulroy Eoin (Orcid ID: 0000-0003-3057-0592)
Bhatia Kailash P (Orcid ID: 0000-0001-8185-286X)
Al-Shimemeri Sohaila (Orcid ID: 0000-0002-2857-4511)

**Video is part of ms.**

# Periodic Limb Movements While Awake (PLMA) as a manifestation of Wearing-Off in Parkinson's Disease: A Case Series and Review of the Literature

Sohaila Alshimemeri, MBBS, FRCPC[1,2], Daniel G Di Luca MD[1], Diana A Olszewska MD, PhD[1], Eoin Mulroy, FRACP[3], Kailash P Bhatia, MD, FRCP[3], Susan H Fox MRCP(UK), PhD[1], Anthony E Lang, MD, FRCPC[1]

1 Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Toronto, Ontario, Canada; Division of Neurology, University of Toronto, Toronto, Ontario, Canada

2 Division of Neurology, Department of Medicine, King Saud University, Riyadh, Saudi Arabia

3 Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK

***Corresponding author**:*

Dr. Anthony E. Lang, Movement Disorders Clinic, Toronto Western Hospital, 399 Bathurst Street, Toronto, ON M5T 2S8, Canada; E-mail: anthony.lang@uhnresearch.ca

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*Abstract*

**Background:** Periodic limb movements while awake (PLMA) are similar to Periodic limb movements in sleep (PLMS) but occurring during wakefulness and seen in association with restless leg syndrome (RLS).

**Objectives:** To describe PLMA as a wearing-off phenomenon in Parkinson's Disease (PD).

**Methods:** We describe four individuals with PD and PLMS, who had associated similar periodic and stereotypic lower extremity movements during wakefulness, thought to be secondary to PLMA, and were highly responsive to dopaminergic treatment.

**Results:** Despite the prevalence of RLS and PLMS in individuals with PD, the presence of similar movements during wakefulness has not been well characterized. The lack of a specific diagnostic criteria poses a significant diagnostic challenge.

**Conclusions:** We describe, for the first time to our knowledge, PLMA as a wearing-off phenomenon in PD. This entity could be classified in the spectrum of "low-dose dyskinesia", as we found that it was highly responsive to dopaminergic treatment.

Periodic limb movements in sleep (PLMS) are characterized by repetitive, periodic and highly stereotypical limb movements during sleep, which may be associated with arousal [1]. PLMS are strongly associated with restless leg syndrome (RLS), which is distinguished by the presence of unpleasant or uncomfortable urge to move the legs that occurs during periods of inactivity and is transiently relieved by movement [2, 3]. Patients with RLS manifest a wide variety of voluntary movements in attempt to relieve the uncomfortable subjective complaints associated with restlessness.

Distinct from the more common voluntary movements performed in an attempt to relieve the subjective RLS symptoms, RLS patients may experience movements similar to PLMS but during wakefulness, referred to as periodic limb movements while awake (PLMA)[4]. Although Parkinson's Disease (PD) has been associated with a higher prevalence of RLS symptoms in general[5], to our knowledge PLMA has not been described in Parkinson's disease as a "low-dose dyskinesia".

***Methods and Results***

In this case series, we describe four individuals with PD and associated PLMA as a possible wearing-off manifestation with significant therapeutic response to dopaminergic therapy (Table 1). Written consents were obtained from the patients prior to video recordings. The details of the cases can be found in the supplementary material accompanying this paper.

***Discussion***

We present four patients with PD and PLMS, who also had associated periodic and stereotypic lower extremity movements during wakefulness, thought to be secondary to PLMA. The videos demonstrate the unique phenomenology, and all four patients demonstrated a clear dose-related response to the dopaminergic medications, which supports the underlying mechanism of a probable wearing-off phenomenon.

Although the clinical manifestations of PLMS and RLS may vary significantly, the current criteria established by the International Restless Leg Syndrome Study Group (IRLSSG) include the presence of PLMA as a motor sign that supports the diagnosis of RLS [2, 4]. These involuntary movements share similar characteristics with movements observed during sleep, although they most often occur in the transition period of falling asleep during the night or while resting during the day [6-8]. As in PLMS, the anatomic distribution of such movements is broad, however most individuals present with brief leg and foot movements lasting from between 1.5 and 2.5 seconds, typically characterized by great toe extension or triple flexion at the ankle, knee and hip [9, 10]. In the case of our patients, there were episodic non-rhythmic jerky movements of the feet (especially with ankle dorsiflexion, sometimes accompanied by milder knee and hip flexion) with variable associated movements of the toes during the wakefulness period. Patient 4 had additional more sustained posturing in the foot and ankle.

Several alternative diagnoses were considered in evaluating these patients. All four individuals had a good response to dopaminergic medications, which suggested a possible wearing-off manifestation. Both RLS and akathisia in the off state are often associated stereotypic leg movements (without the periodicity seen here) secondary to subjective symptoms causing the person to move voluntarily to alleviate the discomfort, which was not the case with our patients.

Prior to witnessing the movements, a form of levodopa-induced dyskinesia was suspected. "Peak-dose dyskinesia" was excluded on the basis of the response to doses of dopaminergic drugs; we postulate that Patient 3 had delayed absorption of his levodopa on the day of observation (see supplements for case details) likely explained by delayed gastric emptying seen in individuals with advanced PD [27]. In fact, the group that introduced the term "low-dose dyskinesia" reported its association with low plasma levels of levodopa after multiple oral doses, caused by failure to properly absorb levodopa, leading to the development of "low-dopa chorea"[28]. "Low-dose dyskinesia" also includes off-period dystonia and diphasic dyskinesia. Both of these usually affect the legs but neither show the characteristic movements seen in our patients, particularly the periodicity. The former manifest more sustained and often painful postures (our patient 4 did show additional posturing that might have been mistaken for this phenotype) and the latter demonstrate repetitive, often stereotyped leg kicking movements but usually of larger amplitude than the movements of PLMA.

A number of epidemiological studies have reported a higher prevalence of RLS in PD, although the underlying mechanism behind such association still remains a matter of debate [5, 11-14]. Previous studies have also discussed the possibility of non-specific "leg restlessness" in individuals with PD rather than true RLS, which would suggest the possibility of a different clinical entity [15]. Moreover, restlessness in several other body parts besides the lower extremities have been described in PD, including arms, chest, back and genital regions [16-19]. The exact pathophysiology of idiopathic RLS is still unknown, although it has been thought to be possibly associated with reduction in striatal D2 receptor levels [20], lower iron levels in the central nervous system [21-23], or even peripheral factors, such as abnormal vascular flow in the affected limbs [24, 25]. Interestingly, three of our patients had an associated axonal neuropathy, which has been previously described in association with RLS [26].

Despite the prevalence of RLS and PLMS in individuals with PD, the presence of similar movements during wakefulness has not been well characterized. Moreover, the lack of specific diagnostic criteria and shared characteristics with non-specific restlessness symptoms pose a significant diagnostic challenge and appropriate recognition by the clinician is essential [15]. Our four patients presented with involuntary movements during wakefulness, initially of unclear etiology. The observed phenomenology characteristic of PLMS strongly suggested the diagnosis of PLMA and this was further supported by the presence of other symptoms of RLS and particularly a history suggestive of PLMS, with strikingly similar movements during the night in all 4 patients.

Although the underlying mechanism generating such movements is unknown, previous studies have demonstrated the role of the spinal cord in PLMS, which is also thought to be similar in PLMA [29-32]. Nevertheless, PLMA has also been associated with relatively long bursts, which supports a possible voluntary prolongation of the initial involuntary movement [33]. It has also been recently proposed that the lack of EMG movement-related cortical potentials preceding the onset of such movements points to a subcortical origin [34], although additional studies are needed to confirm this hypothesis. Finally, studies have demonstrated a shared mechanism between PLMS and spinal flexor withdrawal reflexes, suggesting a possible spinal origin [35]. Supporting this hypothesis, patients with spinal cord pathologies can present with similar triple flexion movements, often also responding to dopaminergic therapies [36-38].

Our study has several limitations. Despite the high likelihood of PLMS in all four patients, we only had diagnostic confirmation by polysomnography (PSG) in one. However, the strong clinical description is highly suggestive of this underlying sleep disorder, especially in the setting

of associated daytime sleepiness with excessive limb movements disturbing sleep. Further, we have not performed the immobilization test (SIT) in our patients, which has been proposed as a potential standard test when classifying and grading the severity of PLMA [39]. Nevertheless, the overall diagnosis of PLMA remains clinical, based on history and physical examination only.

In summary, we present detailed descriptions and video examinations of the atypical and challenging phenomenology of four PD patients with PLMA, expanding the clinical spectrum of OFF manifestations in PD. The response to dopaminergic treatment suggests that these movements could be classified in the spectrum of so-called "low-dose dyskinesia"[40]. Given the fact that these movements developed after long-term treatment with levodopa it is possible that an augmentation phenomenon[3, 41], as occurs in typical RLS, contributed to their development in predisposed patients. Considering the relatively debilitating nature of these movements, clinicians and movements disorders specialists should be aware of this manifestation, especially considering the potential response to dopaminergic therapies. Additional studies are needed to better characterize the relationship between PLMA and PD, including frequency, clinical manifestations, pathogenesis, and best management.

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1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

SA: 1A, 1B, 1C, 3A
DDL: 3A,3B
DO: 3A,3B
EM: 3A,3B
KB: 2C, 3B
SF: 2C, 3B
AEL: 1A, 1B, 1C, 3A, 2C, 3B

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***Ethical Compliance Statement:***

Approval from an institutional review board or ethics committee was not required for this work. Informed patient consent was obtained from all patients for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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***Legends:***

**Video 1.** Intermittent movements consisting of ankle dorsiflexion and plantarflexion, predominantly involving the left lower extremity, and evidence of superimposed low amplitude and slower movements of the toes on the right foot.

**Video 2.** Periodic non-rhythmic jerky movements of the left foot, mostly consisting of ankle dorsiflexion, and associated lower amplitude slower movements of the right toes.

**Video 3**. Intermittent movements consisting of hip flexion, mild knee flexion, and ankle dorsiflexion in the left lower extremity occurring at intervals of 20-35 seconds.

**Video 4.** Intermittent non-rhythmic tonic and jerky movements of the left leg, occurring every 20-30 seconds, involving flexion at the hip and knee and dorsiflexion of the left foot.

**Supporting Data.** Additional Supporting Information may be found in the online version of this article at the publisher's website.

Table1. A summary of the patients' clinical characteristics.

| Patients | Age/Sex | Diagnosis | Comorbidities | Medications | Patient Description | Movement Phenomenology | Presence in sleep | Response to Dopaminergic agents Increase | Others |
|---|---|---|---|---|---|---|---|---|---|
| **Patient 1 (Video 1)** | 75/M | Parkinson's Disease | -Peripheral Neuropathy (Axonal)<br>-Autonomic dysfunction: Urinary complaints, orthostatic hypotension, and sexual dysfunction. | - Levodopa-carbidopa CR 200-50 mg (400 mg/day)<br>- levodopa carbidopa IR 200-50 mg (200 mg daily) | Reported "restlessness sensation" of the legs, starts in the early evening, associated with jumpy and jerky movements of both of his legs, and accompanying posturing of both lower limbs with a cramping sensation | PLMA | Yes | Yes | -Sleep Study confirmed PLMS<br><br>-MRI Brain: No features of MSA. |
| **Patient 2 (Video 2)** | 70/F | Parkinson's Disease | - Peripheral neuropathy (Axonal)<br>- Sjogren's Disease<br>-Restless leg syndrome<br>- Depression | - Levodopa -benserazide 100-25mg (800 mg/day)<br>-levodopa-carbidopa CR 200-50 mg (bedtime)<br>-Duloxetine 60 mg daily | Reported sensation of restlessness in her legs associated with episodes of twitching and jerking movements, involving both of her legs, more on the right side, and lasting a few minutes then subsiding. These movements only occurred when she was lying in bed, and would also be present during the daytime, mostly in the afternoons. | PLMA | Yes | Yes | Seen at a sleep clinic and diagnosed with PLMS and RLS. |
| **Patient 3 (Video3)** | 80/M | Parkinson's Disease | - Peripheral neuropathy (Axonal)<br>- Chronic radiculopathy (L5 and S1 levels) | -Rasagiline 1 mg daily<br>- Levodopa-carbidopa IR 100-25 mg (800 mg daily)<br>- levodopa-carbidopa CR 200-50 mg (bedtime)<br>-Pramipexole 2.25mg (evening)<br>-Gabapentin 300 mg daily | Reported a restless feeling with intermittent jerky movements of his lower limbs at intervals of 20-35 seconds. The movements occurred when he was sitting or lying down, during the daytime, when levodopa is wearing off. | PLMA | Yes | Yes | Sleep study (done at age 72-8 years before development of PLMA) showed:<br><br>- REM parasomnia<br>-No PLMS at that time |
| **Patient 4 (Video4)** | 85/F | Parkinson's Disease | -Restless Leg Syndrome<br>- Atrial Fibrillation | - Levodopa-carbidopa IR 100-25 mg (300 mg daily)<br>- Zolpidem 5 mg (bedtime)<br>- Pramipexole 1.25 mg daily<br>- Melatonin 2 mg (bedtime) | Reported intermittent jerking movements of the lower limbs combined with more sustained posturing particularly on the left, occurring exclusively during the daytime, especially when her levodopa dose was wearing off. | PLMA | Not known | Yes | DaT imaging confirmed bilateral asymmetric (left>right) reduction in striatal tracer uptake |

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Abbreviations: CR= Controlled Release. IR = Immediate Release. Mg = Milligram. PLMS = Periodic Limb Movements in Sleep. RLS= Restless Leg Syndrome. PLMA= Periodic Limb Movements While Awake. ER= Extended Release. DaT =Dopamine Transporter imaging.